

IN BRIEF

BACTERIAL DEVELOPMENT

Living without the cell wall

Bacterial variants that lack a cell wall are known as L-forms and can be induced under conditions that interfere with cell wall synthesis. Claessen and colleagues now report that when filamentous actinomycetes are exposed to osmotic stress they extrude previously undetected cell wall-deficient cells, which they termed S-cells. Formation of S-cells seems to be common in filamentous bacteria, as they occur in *Streptomyces* and *Kitasatospora* species in response to hyperosmotic stress. S-cells extrude from the hyphal tips into the environment, contain DNA and are larger than 2 µm in size (distinguishing them from spores). This cell wall-deficient state is transient as S-cells can switch to the canonical mycelial growth mode, although those switched colonies exhibit developmental defects. Finally, following prolonged exposure to osmotic stress, some cells acquire mutations and convert into L-forms that can proliferate indefinitely in the cell wall-deficient state. In sum, S-cells may represent a newly identified developmental stage that enables actinomycetes to thrive under hyperosmotic stress conditions.

ORIGINAL ARTICLE Ramijan, K. et al. Stress-induced formation of cell wall-deficient cells in filamentous actinomycetes. *Nat. Commun.* **9**, 5164 (2018)

BACTERIAL PHYSIOLOGY

Reprogramming by persisters

Bacterial persisters, which are a subpopulation of transiently antibiotic-tolerant bacterial cells that are slow-growing or growth-arrested, can cause persistent infections. Under laboratory conditions, persisters seem to become dormant; however, Helaine and colleagues show that in the non-growing, antibiotic-tolerant state, *Salmonella enterica* subsp. *enterica* serovar Typhimurium actively subverts host cells. During macrophage infection, *S. Typhimurium* antibiotic persisters retain transcriptional, translational and metabolic activity. Moreover, non-growing *S. Typhimurium* translocates *Salmonella* pathogenicity island 2 (SPI-2) type III secretion system effectors into the macrophage to reprogramme the host cell into a non-inflammatory and infection-permissive state. Thus, the active, non-growing state promotes survival during antibiotic exposure, persistent infections and long-term survival.

ORIGINAL ARTICLE Stapels, D. A. C. & Hill, P. W. S. et al. *Salmonella* persisters undermine host immune defenses during antibiotic treatment. *Science* **362**, 1156–1160 (2018)

FURTHER READING Fisher, R. A., Gollan, B. & Helaine, S. Persistent bacterial infections and persister cells. *Nat. Rev. Microbiol.* **15**, 453–464 (2017)

MICROBIOME

Supporting gut epithelial regeneration

The human gut microbiota includes species that play an important part in gut homeostasis. For example, bacterial species that produce the metabolites butyrate and lactate, such as *Bifidobacterium* and *Lactobacillus*, have been implicated in the maintenance of the colonic epithelium. Research efforts are focusing on understanding the mechanism underlying those beneficial effects. Kweon and colleagues report that lactic-acid-producing bacteria support intestinal epithelial cell regeneration. Bacterial-derived lactate promotes the expansion of intestinal stem cells (ISCs) and epithelial differentiation in vivo and ex vivo. Moreover, a *Lactobacillus plantarum* strain lacking lactate dehydrogenase activity failed to elicit ISC proliferation in mice. Finally, pretreatment with lactic-acid-producing bacteria or lactate protected mice from gut injury induced by radiation and drug treatment.

ORIGINAL ARTICLE Lee, Y.-S. et al. Microbiota-derived lactate accelerates intestinal stem-cell-mediated epithelial development. *Cell Host Microbe* <https://doi.org/10.1016/j.chom.2018.11.002> (2018)

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to the C3 position. Structural analysis showed that TarP, like TarS, forms a trimer, and revealed how the altered binding mode of TarP leads to glycosylation at the C4 position of RboP.

The authors tested whether human serum antibodies discriminate between the two isomeric RboPs. Expression of *tarS* in glycosylation-deficient mutants increased immunoglobulin G (IgG)

binding, whereas expression of *tarP* led to only slightly increased IgG binding, which suggests that TarP attenuates immunogenicity of WTA, and *tarP*-expressing *S. aureus* strains are less likely to induce an immune response. Indeed, mice immunized with purified TarP-glycosylated WTA had lower levels of IgG compared to mice immunized with TarS-glycosylated WTA. Finally, vaccination with TarS-modified or TarP-modified WTA did not protect against subsequent infection with *tarP*-expressing strains compared to mock vaccination.

In summary, this study uncovers a strategy whereby pandemic MRSA clones subvert antibody-mediated immunity. The finding that TarP is crucial for *S. aureus* to evade host defences could guide new treatment strategies, such as the development of TarP inhibitors.

Andrea Du Toit

ORIGINAL ARTICLE Gerlach, D. et al. Methicillin-resistant *Staphylococcus aureus* alters cell wall glycosylation to evade immunity. *Nature* <https://doi.org/10.1038/s41586-018-0730-x> (2018)

IAV particle. The variability in size and composition of the virions that were produced in individual cells was as high as in pooled infection experiments, leading the authors to conclude that the main source of phenotypic variability is imprecise assembly that is inherent in virion biogenesis.

Phenotypic variability can help overcome environmental stresses. Indeed, when cultures were treated with NA inhibitors — which block the cleavage of the host receptor and the release of budding virions — virions with high NA concentrations were preferentially released, whereas larger, HA-rich virions remained on the surface. In summary, variability in size and composition can be a way for IAV to overcome environmental constraints and maintain infection.

Ursula Hofer

ORIGINAL ARTICLE Vahey, M. D. & Fletcher, D. A. Low-fidelity assembly of influenza A virus promotes escape from host cells. *Cell* **176**, 1–14 (2019)

FURTHER READING Ackermann, M. A functional perspective on phenotypic heterogeneity in microorganisms. *Nat. Rev. Microbiol.* **13**, 497–508 (2015)

100-fold between individual virions, and there was a large range in the ratio of HA to NA, which indicates substantial variation in the composition of particles. Furthermore, approximately one-third of virions had low or no NP, which indicates a missing or defective genome, and the proportion of such NP-negative particles was higher in large, filamentous virions than in virions shorter than 1 µm.

To identify the source of phenotypic heterogeneity, the authors analysed virions produced by single cells that had been infected by a single infectious



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